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ART UNIT	**PAPER NUMBER**
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/276,820	Harrington et al
Examiner	**Group Art Unit**
Ram Shukla	1632

[X] Responsive to communication(s) filed on Nov 17, 1999

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

[X] Claim(s) 1-7, 10-15, 20-36, and 58-231 is/are pending in the applicat

Of the above, claim(s) 1-7, 10-15, 20-36, 60-63, 70, 75, 83, 84, 124-127, 133-156, 158, 160, 163, 168, 176, 184-222, 227-231 is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) 58, 59, 64-69, 71-74, 76-82, 85-123, 128-132, 157, 159, 161, 162, 164-167, 169-175, 177-183, 223-226 is/are rejected.

[ ] Claim(s) _____ is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____.

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[X] Notice of References Cited, PTO-892

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

[ ] Interview Summary, PTO-413

[ ] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of invention of group I, claims 58,59, 64-69, 71-74, 76-82, 85-123, 128-132, 157, 159, 161-162, 164-167, 169-175, 177-183, and 223-226 in Paper No. 9 is acknowledged. During a telephonic interview (Paper No 7) on 11-09-99 with applicant's representative, restriction was modified to include claims 25-27 in groups III and IV and it was further clarified that groups III and IV were drawn to plant hosts.

2. Claims 1-7, 10-15, 20-36, 60-63, 70, 75, 83-84, 124-127, 133-156, 158, 160, 163, 168, 176, 184-222, and 227-231 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 73, 77-80, 82, 85-93, 98-106,108-123, 128-132, 180-183, 223-224,226 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 73, 77-80, 82, 85-93, 98-106,108-123, 128-132, 180-183, 223-224, and 226 are drawn to a method of producing expression product of an endogenous cellular gene, activating the expression of or over expressing an endogenous gene by integrating various constructs in a cell in vivo or in vitro or in situ wherein the constructs comprise: a transcriptional regulatory sequence, a transcriptional regulatory sequence linked to an unpaired splice donor sequence and one or more amplifiable markers, a transcriptional regulatory sequence linked to an unpaired

splice donor sequence, one or more amplifiable markers, and viral origin of replication, host cells comprising said vectors and over expressing endogenous genes, and library of cells comprising such vectors and over expressing said genes. Some claims are directed to in vivo activation of gene expression or over expression of a gene or production of expression product of an endogenous gene while in other claims the methods comprise first inducing the expression of a gene, followed by in vitro selecting a cell wherein the expression of an endogenous gene is increased and then administering selected cells to an animal. Some claims are directed to induction of particular genes, such as a growth hormones. For example, claim 90 has a list of more than 70 endogenous genes which are claimed to be activated by the method. Other claims are directed to expression products of the method, library of cells or clone of cells.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. The specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed invention without undue experimentation.

As summarized previously, claimed method are drawn to activation of any endogenous gene or to a list of over 70 genes using a collection of vectors that may comprise only a transcriptional regulatory sequence alone or in combination with splice donor site and one or more selectable markers and one or more promoters. Claimed invention is limited by the fact that it does not use a sequence that will have homology to a known gene, in other words integration of the vectors are not by homologous method but by random integration and non-homologous recombination.

While the specification has provided, diagrams of vectors that comprise claimed sequence elements and protocols to make libraries, PCR and other techniques of making cell lines, library etc., there is no evidence that all the claimed endogenous genes would have been activated by the claimed methods and would have yielded increased production of proteins from

endogenous genes listed. On page 135 of the specification, lines 9-30 continued on page 136 lines 1-3 disclose the results of an experiment of activating expression of transmembrane protein. The specification discloses that in one screening, of eight isolated activated genes 4 encoded known integral membrane protein genes whereas 6 encoded novel genes. However, none of the isolated genes encoded a growth factor, cytokine or hormones or other proteins listed, for example, in claim 90. In yet another example, the specification discloses that of 11 genes isolated, one had sequence homologous to a partially sequenced integral membrane protein gene whereas 9 were novel genes. Again, even this screening did not result in the identification of any of the genes listed, for example, in Claim 90. If an artisan had to target a known gene, for example one in the claimed list, what is the probability that the candidate gene will be activated. If one was targeting insulin receptor or GM-CSF or M-CSF or so on, based on the results disclosed in the specification, one has to conclude that the probability will be zero because none of the listed genes were activated in the provided examples.

Even in the case of a transmembrane protein, while the specification discloses that four of the identified genes were transmembrane genes, there is no disclosure or evidence as to how many fold the expression of the isolated gene was increased or in fact there was any increase in the expression. Furthermore, did the isolated cell expression full length transmembrane protein, was the protein functional, if not what would have been the use of providing such cells to an animal or to a human? When these cells were administered in an animal, would the expression of the transmembrane protein have been same or more or would have ceased? Compared to in vitro method, would the expression of the gene when cells are administered to a human or animal have been high enough to detect the expressed protein. The specification does not provide any guidance to any of these problems as to how an artisan of skill would have been able to make and practice the invention as claimed.

Arguments presented above and the examples disclosed in the specification would indicate that the claimed method results in at random activation and there is no way of finding out which gene has been activated. If so, how can an artisan use this method to activated any endogenous gene, prepare library, isolate cells and use them for administration to an animal if it was not known what gene was activation. Likewise, how can the method be used for in vivo

activation of endogenous gene without knowing which gene will be activated. Furthermore, how can a library be screened if an artisan did not know which genes were activated because without this information for what gene will an artisan screen for? In conclusion, how can a particular endogenous gene be targeted by at random integration of any of the given vectors. In conclusion, the specification does not provide any evidence as to whether the claimed method would have activated any and all the listed endogenous genes.

It is concluded that the specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the claimed invention without undue experimentation.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 64-69, 71-74, 76-82, 85-132, 159-162, 164-175, 177-183 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64-69, 71-74, 76-82, 104-108, 128-132, 159-162, 164-175, 177-183 are indefinite because they are dependent on non-elected invention.

Claim 82 and dependent claims are indefinite because they recite "said gene product" which does not have antecedent basis.

Claim 77, 109-112 and dependent claims are indefinite because it is unclear what is meant by a "genome containing cell"?

Claims 130-132 are indefinite because they are dependent on a claim (89) which does not recite an in vivo method.

Claims 82 is incomplete because it does not recite necessary steps of the claimed method, for example what are the steps of screening or what method of screening will be used.

Claim 85-87, 98, 109, 113, 116, and their dependent claims are incomplete because they do not recite all the necessary steps of the method, for example what method of screening will be used?

Claim 165 is indefinite because it is not unclear what is meant by "comprising genomic DNA", for example genomic DNA of what?

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 58, 59, 64-65, 69, 74, 76, and 225 are rejected under 35 U.S.C. 102(b) as being anticipated by Duyk et al. (Duyk et al. Proc. Natl. Acad. Sci. 87:8995-8999, 1990).

Claims 58 and 64-65 are directed to vectors that comprise a transcriptional regulatory sequence operably linked to an unpaired splice donor sequence and one or more amplifiable marker and wherein said vector does not comprise a homologous targeting sequence. Claims 64 and 65 limit the transcriptional regulatory sequence to a promoter and a viral promoter. Claim 69 is directed to a cell containing the vector of claim 58 while claim 74 limits the cell of claim 69 to an isolated cell. Claim 76 recites a method of making a host cell by introducing the construct of claims 58-62 into cells. Claim 225 recites a vector comprising a transcriptional regulatory sequence operable linked to a gene, a viral origin of replication and an amplifiable marker.

Duyk et al teach a vector pETV-SD wherein the vector comprises a retroviral long terminal repeat operably linked to an exon with donor splice site, SV40 origin of replication and

promoter, and an amplifiable marker (see methods section and figure 1). Duyk et al also teach a host cell wherein said vector is transfected (see table 1) and selection of cells wherein the vector expresses as an episome (see last three lines in third para of col 2 on page 8997). This prior art also teaches isolated single cells that comprise the vector.

Therefore, the invention of claims 58, 59, 64-65, 69, 74, 76, and 225 is anticipated by Duyk et al.

9. Claims 94-97, and 107 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Powell (US 5,688,679, 11-18-1997, filed 10-6-1993).

Claim 94 recites gene expression product of the method of claims 87 or 89 wherein the protein is selected from a group of proteins consisting of erythropoietic, and other more than 70 proteins.

Powell et al teach cDNA that encodes human erythropoietin, recombinant cells producing recombinant erythropoietin and recombinant protein. Since the claim 94 and 95 recites erythropoietin protein which would be not be distinguishable from that of the erythropoietin protein taught by Powell et al, the invention of claim 94 is anticipated by Powell et al.

In the event that the claimed protein is not identical to that disclosed by Powell et al, it is considered that any differences would be the result of minor variations in composition, wherein such variations would have been obvious over the prior art. Thus the claimed invention as a whole was at least obvious over, if not anticipated by, the prior art.

Regarding other gene products of claim 94 and those of 95-97 it is noted that they are all known proteins and their amino acid sequence as well as nucleotide sequence has been determined and known in prior art and reported. Since, the gene products of the claimed invention do not recite any special characteristic of the said gene products, it is interpreted that they would not be different from those known in the prior art.

In the event that the claimed gene products are not identical to those disclosed in the prior art, it is considered that any differences would be result of minor variations, wherein such variants would have been obvious over the prior art. Thus, the claimed invention as a whole was at least prima facie obvious over, if not anticipated by, the prior art.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 66-68, 71-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duyk et al in view of Kaufman 1995 (Short Protocols in Molecular Biology, ed. Ausubel et al. John Wiley & Sons, Inc. 1995, pages 16-58-16-60).

Claims 66-69 recite different types of promoters in the vector of claim 58. Claims 71-72 recite that said vector is integrated into the cellular genome.

The teachings of Duyk et al have been summarized in para 8 above. Duyk et al do not teach that the promoters in their expression vector are CMV immediate early promoter or a non-viral promoter or an inducible promoter. Duyk et al also do not teach that the vectors are integrated into the genome of a cell.

Kaufman reviews strategies for expressing foreign genes into mammalian cells, both for transient expression as well as stable expression. This prior art compares the expression levels from different promoters and expression systems, their use in transient or stable expression and primary uses. Kaufman further teaches that is a selection procedure is applied after DNA transfection, it is possible to isolate cells that have stably integrated foreign DNA into their

genome. This prior art teaches all the methods used for isolating stably transfected cells (see entire article).

At the time of the invention it would have been obvious to one of ordinary skill in the art to modify the vector of Duyk et al by cloning different promoters, such as a viral vector or an inducible promoter as taught by Kaufman and then select cells that were neo resistant, wherein vector DNA would have integrated in the genome of the selected cells with reasonable expectation of success because all the relevant methods are reviewed by Kaufman and different protocols are also provided. An artisan would have been motivated to use a promoter of choice because the expression level of foreign genes under the control of different promoter varies greatly based on the cell type used as discussed by Kaufman (see section on choice of expression system on page 16-60). Furthermore, an artisan would have been motivated to select cells that would integrated the vector in their genome because stable transfectants would have helped in producing cell lines that would have expressed a target coding sequence constitutively and also because, in order to express a certain coding sequence, an artisan would not have to carry out transfection repeatedly. Regarding CMV promoter, it is noted that CMV promoter is yet another commonly used promoter for expressing foreign genes in a mammalian cells.

12. Claims 157, 160, 161, 162, 164, 166, 168-170, 172-173, 174, 177, 178 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duyk et al in view of Anderson (US Patent 5,629,159, 05-13-1997).

Claim 157 recites a vector construct comprising a first promoter driving a positive selection marker, a second promoter driving a negative selection marker, and an unpaired splice donor site wherein when the vector construct is integrated into the genome of an eukaryotic host cell an endogenous gene is said genome is transcriptionally activated and the positive selectable marker is expressed in active form whereas the said negative selection marker is either not expressed or is expressed in inactive form. Claims 160-162 and 164 recite that the vector of claim 157 further comprises one or more amplifiable markers, one or more viral replication factor genes and that the viral replication origin is selected from SV40 ori or EBV ori P.

Teachings of Duyk et al has been summarized previously in para 8. As stated above, Duyk et al teach a vector wherein there has multiple promoters, reporter genes, selectable markers, unpaired splice donor site, and origins of replication (see figure 1). Duyk et al do not teach a vector wherein a negative selection marker is under the regulation of a promoter.

Anderson teaches vectors that can be used for immortalization and disimmortalization of cells by first integrating in the genome of the cell a selection marker and immortalization genes which will lead to immortalization of the cell. Later on, the immortalization gene can be excised of the cell's genome using recombinase and the cells are disimmortalized (see 1-6). Anderson teaches different combination of sequence elements in the organization of vectors wherein all the elements can be continuously linked to each other (figure 1A) while in other case a stop signal can be introduced to separate different reading frames. This way different types of selection methods can be used for isolating cells. They also teach that if one wants to eliminate cells expressing a selection marker , a negative selection marker can be used to kill all the cells that express that negative marker, leaving only those cells which do not express the negative marker (see lines 24-38 in col 5).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the vector of Duyk et al and in place of neo gene clone a negative selection marker such as HSVtk gene, linearize the vector in the cloning site and use the resultant vector in transfecting cells which would allow the integration of the vector in the genome of the cells with reasonable expectation of success. This would, in case the beta-galactosidase gene was expressed because it was joined with a splice acceptor site to include endogenous exon, will allow to select with positive selection marker or beta-galactosidase. However, these cells will have two population of cells, one in which the cells will be expressing both beta-galactosidase and the negative selection gene. To isolate cells in which an endogenous gene with stop codon was trapped, cells expressing negative selection marker could be eliminated by growing cells in the presence of selection agent. An artisan would have been motivated to modify the vector as above because this would have allowed identification of 3'-exons along with the stop codon.

13. Claims 159, 167 and 178 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duyk et al and Anderson as applied to claims 58, 59, 64-65, 69, 74, 76, 225, 157, 160, 161, 162, 164, 166, 168-170, 172-173, 174, 177, 178 above, and further in view of Devine et al (US 5,677,170, 10-14-1997).

Claim 159 recites that the vector of claim 157 further contains one or more transposition signals. Claim 167 recites the host cell comprising the vector of claim 159.

The teachings of Duyk et al and Anderson has been summarized in paras 8 and 12. None of these teach to include transposition signal in their vectors.

Devine et al teach efficient methods of creating artificial transposons and inserting these transposons into plasmid targets in vitro. These can be used to introduce any functional or non-functional DNA cis elements, sequence or combination into another segment of DNA (see lines 11-67 col 10 continued in cols 11 and 12).

At the time of the invention, it would have been obvious to an artisan of ordinary skill in the art to modify the vector of Duyk et al by including transposition sequences of Devin et al with reasonable expectation of success, linearize the vector, transfect in a cell and select the cells that would have expressed beta-gal but not the negative selection marker because Duyk et al, Anderson and Devine et al teach all the necessary methods and sequences. An artisan would have been motivated to include the transposon in the vector, create a library of cells that comprise the vector because due to the random integration of the vector in the genome of cells, cells would have integrated the vector in different exons and thus trap vectors that could then be isolated.

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner

can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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